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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,463	06/27/2003	James W. Ryan	JR-10,003-US	6428

25538 7590 06/24/2009

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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
06/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action

1. Amendment filed 5/30/2008 is acknowledged. The amendment (see claims 7 for example) is **NOT entered** for raising new issues which will require further consideration and/or search.

Claim 7, (currently amended), recites "An isolated nucleic acid molecule 20-51039 contiguous nucleotides in length consisting of a reverse or forward strand of a region of SEQ ID NO:4, wherein said region is selected from the group consisting of a 5'-non coding region ~~depicted in~~ between nucleotides 51039-41739 of SEQ ID NO:4…".

Newly drafted claim entirely changes the scope of the claim, which will require further consideration and/or search.

2. Applicants arguments concerning the new matter rejection is considered but not found to be persuasive because no explicit and/or unambiguous support for the recited language has been provided. Therefore, all prior rejections are maintained for reasons of record, which rejections and prior arguments are reproduced here.

Clearly pointing to support in the instant specification as filed may result in further search of the amended claims, reconsideration of rejections and possible allowable subject matter.

Claims 7, 10, 12, 14-18, 20, 22-25 and 30-38 are pending. Claims 12, 14, 22, 23 and 32 have been previously withdrawn.

3. Claims 7, 10, 15-18, 20, 24, 25, 30 and 31 are under consideration.

4. Applicant's arguments filed with the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

5. Any objection or rejection of record not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

6. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

> terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 10, 15-18, 20, 24, 25, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For the purpose of the new matter rejection, claims and specification filed 6/27/2003 are being considered as original filed subject matter. Any amendments to the claims subsequent to this date without a proper basis in the instant specification will be considered as new matter lacking written description.

Claim 7, with dependent claims 10, 15-18, 20, 30 and 31, has been amended on March 3, 2005 and August 29, 2005 and claim 24, with dependent claim 25, was added on March 3, 2005 and amended on August 29, 2005 to recite "wherein a sequence segment comprising 41738-9502 of SEQ ID NO: 4 encodes human mouse double minute 2 homolog depicted in SEQ ID NO:2, … a region comprising a dinucleotide of the following group: 41739-41738, ……and/or 9504-9503" (lines 12-15 of claim 7). Applicant does not indicate and the examiner is unable to locate adequate support in the specification for such positions/ranges in SEQ ID NO: 4.

It is also noted that claim 7, starting from line 17, indicate ***nucleotide ranges*** for various binding sites for huMDM2, location in SEQ ID NO: 4 (claims filed 9/14/2008), pages 2-8. However, there is no basis for these nucleotide ranges (For Example: AP1_C: 36-46, 2876-2886 ; AP4_Q5: 7944-7980 (starting on page 2 of claims filed 9/14/2008……to….nucleotides ranges for the binding sites on pages 3, 4, 5, 6, 7 & 8).

Thus there is no indication that the specific segments or ranges were within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Applicant asserts that there is more man adequate support in the specification for claims 7, 10, 15-18, 20, 30 and 31 and in particular, the sequence segment 41738-9502. First, Applicant notes that page 4, lines 25-30 states:

The invention is directed to isolated genomic polynucleotide fragments that encode ...human mouse double minute 2 homolog, which in a specific embodiment are...human mouse double minute 2 homolog genes, as well as vectors and hosts containing these fragments and polynucleotide fragments hybridizing to non-coding regions, as well as antisense oligonucleotides to these fragments.

Further, the specification on page 14, lines 29-33 states:

The present invention also relates to nucleic acid constructs comprising a polynucleotide sequence containing the exon/intron segments of the ..... human mouse double minute 2 homolog gene (nucleotides 1-51039 of SEQ ID NO:4).

Table 2 on page 10 of the specification shows "exon/intron organization of the human mouse double minute 2 homolog gene.., in SEQ ID NO:4, 51039 base pairs; nucleotides 99541-150579 in the genomic clone of accession no. AC025423 (reverse strand cloning)". Exon 1 according to Table 2 begins at nucleotide 40646 of SEQ ID NO: 4 and the stop codon terminates at nucleotide 10091 of SEQ ID NO:4. Clearly, nucleotides 41738-9502 of SEQ ID NO: 4 would constitute a sequence segment that encodes human mouse double minute 2 homolog protein.

A region encompassing the dinucleotide 41739-41738 would be within the 3'-noncoding region and would thus constitute a fragment containing a 3'non-coding region. In conclusion, there is adequate support for the phrase in claim 7 "wherein a sequence segment comprising 41738-9502 of SEQ ID NO: 4 encodes human mouse double minute 2 homolog depicted in SEQ ID NO: 2, ... a region comprising a dinucleotide of the following group: 41739-41738, ... ". Further, there is adequate support for claim 24 directed to an isolated nucleic acid molecule 20-5000 nucleotides in length consisting of a reverse or forward strand of a contiguous exon-intron region or intron-exon region between nucleotides 41738-9502 of SEQ ID NO: 4 and claim 25 directed to "an isolated nucleic acid molecule 20-5000 nucleotides in length comprising nucleotides 41739-41738 ....". Further, claims 10, 15-18, 20, 24, 25, 30 and 31

ultimately depend from claim 7. Thus, arguments made with respect to claim 7 would apply to these claims as well. Therefore, Applicant respectfully request that the rejection under 35 USC 112, written description be withdrawn.

Response: Applicants arguments are considered but not found to be persuasive because the specification as originally filed does not teach the specific ranges that related to the specific dinucleotide ranges or the specific *'exon/intron'* organization in term of the specific nucleotide range(s).

Based upon the teachings of Table 2, on page 10, wherein Exon 1 begins at nucleotide 40726 of SEQ ID NO: 4 and the stop codon terminates at nucleotide 10091 of SEQ ID NO: 4. However is it not clear that nucleotides 41738-9502 of SEQ ID NO: 4 would constitute a sequence segment that encodes human mouse double minute 2 homolog protein. Similarly, the region comprising a dinucleotide i.e., nucleotides '41739-41738', does not have no basis in the instant specification.

The rejection is maintained for all the above reasons

7. ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7, 10, 15-18, 20, 24, 25, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muzny et al. in view of Vogelstein et al.

Muzny et al. (150579 bp, GenBank accession AC025423, March 9, 2000, cited on form PTO-892 mailed 12/1/04) teach the sequence of human chromosome 12 comprising the sequence of SEQ ID NO: 4 (51039 bp) of the instant invention.

Vogelstein et al. (US Patent 5,411,860, GenBank accession NM_002392, cited on form PTO-892 mailed 12/1/04) teach cloning, functional expression and chromosomal localization of human mouse double minute (MDM2) homolog. They teach cDNA (SEQ ID NO: 1) encoding human MDM2 homolog (SEQ ID NO:2, 491 amino acids) that is 100% identical to the human MDM2 homolog of the instant invention (SEQ ID NO:2). Using a labeled probe, they localized the gene encoding said human MDM2 homolog to chromosome 12q12-14 (column 5, lines 2-13; the description of SEQ ID NO: 1 in the Sequence Listing). Vogelstein et al. teach that human MDM2 binds to oncogene p53 and is diagnostic of tumorogenesis (e.g., column 3, lines 20-35). SEQ ID NO: 1 taught by Vogelstein et al. comprises 5' non-coding region consisting of nucleotides 1-311. The elected species of 41739-41738 correspond to exon-intron junction within the genomic DNA corresponding to said 5' non-coding region.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use said cDNA taught by Vogelstein et al. to identify the genomic DNA that encodes the human MDM2 homolog of SEQ ID NO: 2 on chromosome 12. The motivation is provided by Vogelstein et al. who teach that it binds to oncogene p53 and is diagnostic of tumorogenesis (e.g., column 3, lines 20-35). The state of the art provides various techniques for obtaining genomic DNA using cDNA probes that are usually labeled. The comparison of genomic and cDNA would result in the identification of regions comprising exon-intron and intron-exon junctions within coding and non-coding regions. One of ordinary skill in the art would have been motivated to use said non-coding regions or fragments thereof of at least 20 nucleotides and up to 5000 or 51039 nucleotides (the entire length of SEQ ID NO: 4) nucleotides for detecting splice variants of the genomic DNA encoding human MDM2 homolog in genomic nucleotide samples from an individual, for example. As a matter of convenience a non-coding region such as an exon-intron or intron-exon region or fragments thereof can be present in a kit or on a solid support. Further, said support can be a microarray according to a customary use of nucleic acid molecules in the art.

Response to Arguments (previous)

Applicant's arguments filed March 2, 2008 have been fully considered but they are not persuasive.

With regard to the 103(a) rejection, Applicant's arguments can be summarized as follows: 1) Muzny contains a small portion of chromosome 12, where the location of the MDM2 gene was indicated by Vogelstein as 12q12-14 while Applicant found it on 12q and 2) the MDM cDNA constitutes only 1.6% of the clone disclosed by Muzny, therefore it would be undue experimentation to locate the MDM2 gene and identify its exon-intron junctions.

Applicant argues "In Appellant's view, it would not have been obvious to combine the disclosure of Muzny and Vogelstein given that there was no suggestion to do so. Muzny merely contains just a small portion of chromosome 12 DNA. Chromosome 12 is about 130 million base pairs long and is believed to contain several hundred genes (by analysis after 2001 and after the Applicant discovered the human MDM2 homologue gene). Muzny et al knew that clone AC025423 (from 1VII-61102) was from chromosome 12 but there is no evidence in the NCBI report of a sub-assignment to the p- or q-arm. Further, there is no evidence that Muzny knew whether the clone did or did not contain one or more genes and particularly whether it contained the gene encoded by SEQ ID NO:4. As will be discussed in further detail below, the MDM2 cDNA constitutes just 1.6% of the clone disclosed by Muzny. Undue experimentation would have been required not only to locate the MDM2 gene but also identify exon-intron junctions" (Supplemental Appeal Brief of 3/2/08, page 11).

Applicant further argues Second, Appellant asserts that there would not be a reasonable expectation of success of obtaining the claimed non-coding sequences of SEQ ID NO: 4 in view of the cited references. Vogelstein placed the human MDM2 homologue gene at 12q12-14. As noted above, there was actually a previous disclosure stating that the MDM2 was located between 12q14.3-15 (see, for example, Andersen et al., 1996, Mammalian Genome 7: 780-783 and Bureau, 1995, Genomics 28: 109-112, submitted and disclosed in previous response attached hereto as Exhibit 1). However,

given the conflicting locations published as of the priority, one of ordinary skill in the art would not have known which location was actually correct" (Brief, page 14).

This is not agreed with because the actual location does not matter as long as it is a part of the Muzny sequence, which it is. Applicant did not need to separate the Muzny sequence into the fragments containing different arms of chromosome 12. In fact, Applicant did not isolate the fragment 12q12-14 or 12q14.3-15. He run cDNA against the genomic DNA disclosed by Muzny and found the location of the gene where it was. This experiment was performed according to the knowledge and the state of the art as evidenced by Watson et al. Watson et al. teach that "once the first genes were cloned, introns were identified by comparing the cloned genomic DNA with the corresponding cloned cDNA" ("Recombinant DNA", page 137, 2nd column, form PTO-892 mailed 4/16/07). Applicant's argument would be convincing if the exact location would need to be known before the comparison of the genomic and the cDNA is made. This is not the case because the work is done on the genomic DNA that is known without fragmentation thereof. Applicants further argues that "Watson would not apply in this case since in Watson, the genes themselves were actually cloned" (ibid, page 18, last sentence). This is not persuasive because Muzny provided the piece of the genomic DNA containing the requisite gene. Having the cDNA, it does not require undue experimentation to identify the fragment of the genomic DNA corresponding to the gene and exon-intron locations within said gene.

The second type of Applicant's arguments concerns with the fact that the cDNA constitutes only 1.6% of the genomic DNA. While a large quantity of the experimentation may be involved, it is not undue because sufficient guidance and knowledge are provided by the art.

New Arguments:

Applicants present no new arguments than the arguments already responded to and which are found to not persuasive. The rejection is therefore maintained.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272 0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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June 22, 2009